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Review

Clostridium tertium in neutropenic patients: case series at a cancer institute

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SUMMARY

Objective: *Clostridium tertium* is considered an uncommon pathogen in humans, but is a cause of bacteremia in patients with underlying hematological malignancies and neutropenia. A case series highlighting 10 years of experience with *C. tertium* as a cause of bacteremia in this population is presented; the cases were seen at a National Cancer Institute designated cancer center.

Methods: Institutional review board approval was obtained prior to the start of the study. All cases of *C. tertium* bacteremia seen at H. Lee Moffitt Cancer Center and Research Institute from 2005 to 2015 were reviewed. The study population was identified by positive blood cultures obtained from the microbiology laboratory over the same time period.

Results: Seven patients were found to have had *C. tertium* bacteremia. These patients had a temperature of >38.3 °C at the time of diagnosis and severe neutropenia. All patients had a history of hematological malignancy, five having acute myeloid leukemia and two having myelodysplastic syndrome. All of the patients' blood cultures cleared within ≤3 days of antibiotic therapy.

Conclusions: The unusual susceptibility pattern of *C. tertium*, with resistance to beta-lactams and clindamycin, likely explains its presence in immunosuppressed patients. Vancomycin remains the drug of choice. The pathogen continues to have a low virulence and a low mortality when treated appropriately.

1. Introduction

Clostridium species are a diverse group of anaerobic, Gram-positive, endospore-forming bacilli known to cause botulism, tetanus, gas gangrene, and necrotic enteritis in humans. *Clostridium tertium* is a non-exotoxin-producing, aerotolerant species that is considered an uncommon pathogen in humans.[1] *C. tertium* was initially isolated by Herbert Henry from war wounds in 1917, and was recognized as a human pathogen when cases of bacteremia were reported in 1963.[2,3] This bacterium is found in soil, animal and human gastrointestinal tracts, and the commensal flora of the oral cavity. Infections with *C. tertium* have been described in the literature with various clinical presentations, including enterocolitis, septicemia, pneumonia and empyema, spontaneous peritonitis, abdominal and cutaneous abscesses, meningitis, gas gangrene, and septic arthritis.[1,4,5]

A case series of *C. tertium* bacteremia in patients with underlying hematological malignancies is presented. This series represents a 10-year experience at a National Cancer Institute designated cancer center, and the aim was to share this experience of *C. tertium* as a true cause of clinical infection in cancer patients.

2. Materials and methods

Institutional review board approval was obtained prior to the start of the study. In an effort to further study *C. tertium* bacteremia, all cases of *C. tertium* bacteremia that occurred at H. Lee Moffitt Cancer Center and Research Institute from April 10, 2005 to April 8, 2015 were reviewed. The study population was identified by positive blood cultures obtained from the microbiology laboratory over the same time period. All culture results were identified by the microbiology laboratory at the Moffitt Cancer

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Center. Retrospectively, records were reviewed for demographic, clinical, and bacteriological data, including sex, age, underlying disease and history of chemotherapy, symptoms, absolute neutrophil count (ANC), antibiotic therapy, and clinical outcome. Neutropenia was defined as an ANC of $<0.5 \times 10^9$/l. Neutropenic fever was defined as a patient with neutropenia and a one-time fever of ≥38.3 °C or a fever of ≥38 °C sustained for more than 1 h.

The identification of microorganisms was performed using standard microbiological methods. The patient's blood was inoculated into a bioMérieux BacT/Alert standard aerobic bottle and standard anaerobic bottle. Once the anaerobic bottle was flagged as being positive by the instrument, it was Gram-stained. The bottle was then subcultured onto a blood, chocolate, and CDC anaerobic agar plate. Once the anaerobic plate showed growth of an anaerobic Gram-positive rod, an IDS Rapid ANA II identification panel was set up for identification as *C. tertium*. anaerobic susceptibilities are performed at the hospital.

2.1. Case presentation

Please refer to the following link to review a detailed presentation of the cases: https://sites.google.com/site/clostridiumtertium/.

3. Results

Seven patients were found to have had *C. tertium* bacteremia between April 2005 and 2015 at the cancer institution, all of whom were neutropenic. Interestingly, six patients (85%) had received CLAG-M chemotherapy (cladribine, cytarabine, filgrastim, and mitoxantrone) within 7–14 days before the onset of *C. tertium* bacteremia. All seven patients (100%) had a temperature of ≥38.3 °F at the time when *C. tertium* bacteremia was diagnosed, as well as severe neutropenia with an ANC of $<0.2 \times 10^9$/l. All patients had a history of hematological malignancy, five having acute myeloid leukemia and two having myelodysplastic syndrome. Four patients had gastrointestinal symptoms including diarrhea, nausea, vomiting, and abdominal pain; two patients had respiratory symptoms including dyspnea and hypoxia; one patient remained asymptomatic. Two patients had computed tomography scans of the abdomen performed; none of them identified the potential source of infection and none of them demonstrated colitis despite the presence of gastrointestinal symptoms. Blood cultures from three patients were polymicrobial with *Enterococcus* species. All of the patients' blood cultures cleared within ≤3 days of antibiotic therapy. Five patients died within 4 months after the isolation of *C. tertium* (Table 1).

4. Discussion

Clostridium species account for 0.5–2% of all clinically significant bacteremia, with *Clostridium perfringens* being the most common isolate. *C. tertium* is the second most common Clostridium bacteremia at the study institution after *C. perfringens* and has been seen as a cause of true clinical infection especially over the last 2 years. *C. tertium* has been traditionally considered non-pathogenic.[6–8] It is now increasingly reported as a human pathogen, having a strong association with septicemia in patients with neutropenia and hematological malignancies.

Unlike other *Clostridium* species, *C. tertium* does not produce exotoxins; therefore the pathogenesis of infection is not well understood. It has been postulated that compromise of the intestinal mucosa heightens the risk of *C. tertium* translocation into the systemic circulation.[1,9] Additionally, chemotherapy agents can lead to inflammation and abrasion of the intestinal mucosa, which may explain why patients with a hematological malignancy who are undergoing chemotherapy have an increased susceptibility to infection.[4]

Common characteristics of *C. tertium* infection included fever and generalized gastrointestinal complaints such as abdominal pain, diarrhea, rectal bleeding, and nausea. However, in some cases, patients with *C. tertium* infection were completely asymptomatic. Additionally, most patients were neutropenic without a defined source of infection.

It can be difficult for laboratories to correctly identify *C. tertium* isolates, as it is aerotolerant and can grow weakly under aerobic conditions. Due to this, *C. tertium* is often confused with *Bacillus* species, although *C. tertium* is catalase-negative and only produces spores under anaerobic conditions, while *Bacillus* species are catalase-positive and produce spores under aerobic conditions.[6,9–11] This may cause delays in treatment or patients may receive incorrect antibiotic therapy.[10]

C. tertium has been shown to be sensitive to fluoroquinolones, imipenem, vancomycin, and trimethoprim–sulfamethoxazole, and resistant to other beta-lactams and clindamycin. *C. tertium* isolates can either be sensitive or resistant to metronidazole.[4,10] *C. tertium* is mostly resistant to broad-spectrum cephalosporins, and given the difficulty in identifying *C. tertium* isolates, empiric therapeutic strategies may fail in hospitalized patients with sepsis.[6,10,12] Therefore, standard therapeutic regimens for the treatment of septicemia may be inadequate for *C. tertium*. There is limited literature regarding the duration of antibiotic therapy, although it is believed that approximately 15 to 27 days of treatment is sufficient.[9]

Table 1
Clinical summary of seven patients with *Clostridium tertium* bacteremia

Patient	Sex/age (years)	Underlying disease	Source of infection	Days with positive *C. tertium* blood cultures	Isolates in addition to *C. tertium*	Antibiotics received	Survived
1	F/82	Acute myeloid leukemia	Abdomen	3	None	Vancomycin, piperacillin–tazobactam, ciprofloxacin	No
2	F/36	Acute myeloid leukemia	Abdomen	1	None	Vancomycin, piperacillin–tazobactam, metronidazole, clindamycin	No
3	F/42	Acute myeloid leukemia	Unknown	2	None	Piperacillin–tazobactam, clindamycin	Yes
4	M/55	Myelodysplastic syndrome	Abdomen	3	*Enterococcus faecium*	Cefepime, vancomycin, piperacillin–tazobactam	No
5	M/60	Acute myeloid leukemia	Unknown	2	*Enterococcus faecium*	Vancomycin, metronidazole	No
6	M/69	Myelodysplastic syndrome	Unknown	2	*Enterococcus gallinarum*	Cefepime, vancomycin, piperacillin–tazobactam	No
7	M/60	Acute myeloid leukemia	Unknown	2	None	Ciprofloxacin, cefepime, vancomycin	Yes

F, female; M, male.

C. tertium is known to have low virulence due to being a non-exotoxin-producing bacterium, unlike *Clostridium septicum* and *C. perfringens*, which are subgroups of the *Clostridium* species known to cause spontaneous and traumatic myonecrosis, respectively.[3,13,14] Bacteremia with *C. septicum* and *C. perfringens* can lead to systemic toxicity and septic shock, with a mortality rate greater than 60%, secondary to the toxins produced by these species.[8,15,16] Therefore, it is not entirely clear from the literature whether *C. tertium* is a true pathogen or merely a contaminant. Additionally, *C. tertium* has been isolated from polymicrobial blood cultures, making the significance of *C. tertium* bacteremia further indistinct.[6,9]

Most patients with *C. tertium* bacteremia have been neutropenic due to chemotherapy, without a defined source of infection.[17] A literature review demonstrated a summary of 42 cases with *C. tertium* bacteremia, of which 38 patients were neutropenic from chemotherapy. In these cases, patients developed *C. tertium* bacteremia within several days after becoming neutropenic.[12] However, there have been rare cases of *C. tertium* bacteremia in non-neutropenic patients, such as patients with end-stage liver disease from chronic alcohol use, systemic lupus erythematosus on high-dose steroids, and inflammatory bowel disease. Despite the low pathogenic potential of *C. tertium* species, effective treatment should not be delayed.[9]

Although *C. tertium* is rare with low virulence, it appears to be a cause of true clinical infection in neutropenic patients.[6] Of the cases presented, all patients with monomicrobial bacteremia had a high-grade fever and symptoms that resolved after the initiation of appropriate antibiotic therapy,[17] demonstrating that *C. tertium* bacteremia does cause clinical disease. Nevertheless, the mortality related to *C. tertium* bacteremia that is treated appropriately seems to be low. In patients with neutropenia, especially when there is evidence of gastrointestinal involvement,[11] clinicians should be encouraged to consider *C. tertium* when Gram-positive rods are found in blood culture, and to initiate appropriate antimicrobial therapy such as vancomycin.

In conclusion, *C. tertium* bacteremia is a rare pathogen in neutropenic patients. It is often mistaken for *Bacillus* species, which may cause delays in treatment. Although uncommon, the presence of *C. tertium* bacteremia should prompt a high suspicion for disruption to the gastrointestinal tract mucosa. In all of the cases reported at this cancer institution, blood cultures cleared with antibiotic therapy; no patient died as a result of *C. tertium* bacteremia. Therefore, the pathogen continues to have a low virulence and a low mortality when treated appropriately. *C. tertium* is known to be a true pathogen in patients with underlying hematological malignancies and neutropenia. It is hoped that this case series will assist clinicians when encountering this pathogen as a true cause of clinical infection.

Conflict of interest: None of the authors or their immediate family members has an involvement in or affiliation with an organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this article.

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